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TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
JUN 79 A W SINGER

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UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT AI3-36329a
1-[(6-METHYL-3-CYCLOHEXEN-1-YL)CARBONYL]PIPERIDINE
STUDY NO. 75-51-0101-79
APRIL 1978 - JUNE 1979



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6 Topical Hazard Evaluation Program of Candidate Insect Repellent AI3-36329a, 1-[<u>(6-Methyl-3-cyclohexen-1-yl)carbonyl</u>]piperidine, S- 79 April 1978 - June 1979		5. TYPE OF REPORT / PERIOD COVERED rept. Final - Jun 79 PERIODICITY AND REPORT NUMBER
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A preliminary hazard evaluation of AI3-36329a was performed by means of laboratory animal studies using rats, rabbits and guinea pigs. The technical grade compound caused mild primary skin and eye irritation in rabbits, and produced a photoirritation reaction. It did not sensitize guinea pigs or prove to be an acute ingestion hazard. Ethanol solutions of AI3-36329a also produced primary skin irritation. It was recommended that AI3-36329a 1-[<u>(6-Methyl-3-cyclohexen-1-yl)carbonyl</u>]piperidine, not be approved for further testing.		



DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

CPT Singer/lm/AUTOVON
584-3980

28 SEP 1978

HSE-LT-T/WP

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellent
AI3-36329a, 1-[(6-Methyl-3-cyclohexen-1-yl)carbonyl]piperidine,
Study No. 75-51-0101-79, April 1978 - June 1979

Executive Secretary
Armed Forces Pest Control Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

A preliminary hazard evaluation of AI3-36329a was performed by means of laboratory animal studies using rats, rabbits and guinea pigs. The technical grade compound caused mild primary skin and eye irritation in rabbits, and produced a photoirritation reaction. It did not sensitize guinea pigs or prove to be an acute ingestion hazard. Ethanol solutions of AI3-36329a also produced primary skin irritation. It was recommended that AI3-36329a 1-[(6-Methyl-3-cyclohexen-1-yl)carbonyl]-piperidine, not be approved for further testing. If, however, this compound presents a significant improvement in pest repellent properties over existing compounds, it is suggested that it be purified with activated charcoal and resubmitted in its proposed use formulation and/or concentration.

FOR THE COMMANDER:

1 Incl
as (5 cy)

BRENDAN E. JOYCE, Ph.D.
COL, MSC
Director, Laboratory Services

CF:
HQDA (DASG-PSP)
Cdr, HSC (HSPA-P)
Dir, Advisory Ctr on Tox, NRC
Supt, AHS (HSA-IPM)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region



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HSE-LT-T/WP

TOPICAL HAZARD EVALUATION PROGRAM
OF CANDIDATE INSECT REPELLENT AI3-36329a
1-[(6-METHYL-3-CYCLOHEXEN-1-YL)CARBONYL]PIPERIDINE
STUDY NO. 75-51-0101-79
APRIL 1978 - JUNE 1979

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man-Research Laboratory, Gainesville, Florida, 12 April 1978.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration; titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCES.

a. Toxicology Division Procedural Guide, USAEHA, 1972, revised 1976.

b. Letter, USDA - Agricultural Research Service, Northeastern Region, Organic Chemical Synthesis Laboratory, Beltsville, Maryland 20705, 15 May 1979.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellent AI3-36329a.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent AI3-36329a, 1-[(6-Methyl-3-cyclohexen-1-yl)carbonyl]piperidine, was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:^{*†}

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1972 - second printing 1974.

† The experiments reported herein were performed in animal facilities, fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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TABULAR PRESENTATION OF DATA

Test	Results	Interpretation
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SKIN IRRITATION STUDIES

Rabbits

Single 24-hour application
to intact and abraded
skin of New Zealand
White rabbits.

0.5 ml technical grade
compound applied to each
of six rabbits.

Compound AI3-36329a
produced mild irritation
of the intact skin and
to the skin surrounding
an abrasion.

USAEHA Category II
(ref Appendix).

EYE IRRITATION STUDIES

Rabbits

Single 24-hour application
of 0.1 ml technical grade
compound to one eye of
each of six New Zealand
White rabbits.

Compound AI3-36329a
produced mild corneal
injury in five of six
rabbits, and mild
conjunctival irritation
in all six rabbits.
All were normal at
7 days.

USAEHA Category C
(ref Appendix).

APPROXIMATE LETHAL DOSE (ALD)

Oral

Rats (male) - no diluent

ALD > 4300 mg/kg

Presents little
lethal hazard from
accidental ingestion.

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Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		

Rabbits

A single 0.05 ml application of a 25 percent (w/v) solution of the compound and a 10 percent (w/v) oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.

A 25 percent solution of AI3-36329a in ethanol caused a photochemical irritation reaction under test conditions.

Compound AI3-36329a caused a photochemical irritation reaction under test conditions and may cause a similar photochemical irritation in humans.

Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.

Control

Following UV exposures of the rabbits, 0.05 ml of test compound, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.

All ethanol mixtures of AI3-36329a produced mild irritation regardless of whether sites were exposed to UV light or not.

Ethanol solutions of AI3-36329a may cause irritation to human skin.

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Distribution/
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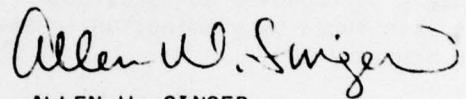
Test	Results	Interpretation
SENSITIZATION STUDIES		
Guinea Pigs (Male)		
Intradermal injections of a 0.1 percent solution (w/v) of AI3-36329a or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.		
Ten test guinea pigs were given 10 sensitizing doses of 0.1 ml over a 3-week period. After 2 weeks' rest, they were challenged with a 0.05 ml ID injection of test compound.	Challenge dose of AI3-36329a did not produce a sensi- tization reaction.	Compound AI3-36329a did not produce a sensitization reaction under test conditions and is not expected to produce a sensiti- zation reaction in man.
Ten positive control guinea pigs were sensitized over 3 weeks to DNCB. After 2 weeks' rest, they were challenged with a 0.05 ml ID injection of DNCB.	Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs	DNCB produced a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer

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5. CONCLUSION. Technical grade compound AI3-36329a caused mild skin and eye irritation. Ethanol solutions of AI3-36329a caused mild irritation before UV exposure, which became even more severe after UV exposure. Similar reactions in man are possible.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that AI3-36329a, 1-[(6-Methyl-3-cyclohexen-1-yl)carbonyl]piperidine, not be approved for further testing as a candidate insect repellent. However, if this compound presents a significant improvement in pest repellent properties over existing compounds, it is suggested that it be purified through activated charcoal and resubmitted at its proposed use formulation and/or concentration.



ALLEN W. SINGER
CPT, VC
Laboratory Veterinary Officer
Toxicology Division

APPROVED:



ARTHUR H. McCRESH, Ph.D.
Chief, Toxicology Division

APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals. prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

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D. Compounds producing moderate injury to the cornea. INTERPRETATION:
Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition
producing some injury to the conjunctiva. INTERPRETATION: Should be used
with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the
conjunctiva. INTERPRETATION: Should be used with extreme caution. It is
recommended that use be restricted to areas other than the face.